REMARKS

The only issues outstanding in the Final Rejection mailed August 5, 2008, are the rejections under 35 U.S.C. §§ 112, 102 and 103. Reconsideration of these issues, in view of the following discussion, is respectfully requested. Claim 1 has been amended to correct the inadvertent omission of a word. Entry of the amendment, which does not change the scope of the claim, is respectfully requested.

Rejection to 35 U.S.C. § 112

Claims 1-7 and 10 have been rejected under 35 U.S.C. § 112, first paragraph. Reconsideration of this rejection is respectfully requested.

It is argued, at page 2 of the Office Action, that the claims contain subject matter which is not described in the specification. Specifically, it is argued that there is no support in the specification for the recitation in claim 1 of "elution" chromatography, nor for the recitation that, in the process, "suitable elution chromatography parameters for separating the biological sample and to bio-molecules are ascertained." Applicants respectfully disagree that the specification does not teach both the use of elution chromatography, and the determination of relevant elution chromatography parameters. To the extent that the Office Action believes that it is necessary to find the *exact* phrase in the claims somewhere in the specification, it is submitted that this is not the relevant standard. For example, the Federal Circuit's predecessor court has held, *In re Wertheim et al.*, 541 F2d. 257, 191 U.S.P.Q. 90 (CCPA 1976), that the standard for written description is whether a specification teaches one of ordinary skill in the art that the inventors invented the invention which is later claimed, and notes that express written support is not needed where that concept is taught. The present specification clearly teaches the concept of elution chromatography, and of determining suitable elution chromatography parameters. For example, at page 4, lines 1-20 in the specification, it is stated that the invention is "suitable for the automated search for suitable chromatography media and the associated buffer *and elution conditions* for the purification of peptides and proteins, but also other bio-molecules." The noted portion of the specification continues that the "bio-molecules absorbed onto the gel particles are

re-dissolved from the gel particles by means of a suitable elution solution (mobile phase)." The passage concludes that, "it is possible to determine a wide variety of chromatography parameters, such as, for example, gel media, buffers, Ph, solvent additives or substances for the stabilization of bio-molecules." Other portions of the specification also make it amply clear that the inventions is directed to the determination of elution parameters:

line 4 of the abstract: "solution for desorption (elution) of the bio-molecules bound to the gels."

line 6 of the abstract: "of the unbound bio-molecules and/or the eluates."

page 3, line 26 of the specification: "Of such solutions and substances (henceforth referred to as elution solutions) is the ability for desorption (elution) of the biological sample from the chromatography gel,"

page 3, line 29: "that the bio-molecules bound to the chromatography gel have no or only low affinities to the chromatography gel after addition of the elution solution."

page 5, line 5: "To this end, the multiwell plates may already be prefabricated with chromatography media for binding the biological sample (group B materials and a set of very different chromatography media (solutions of any composition) for elution (group NB materials)."

page 5, line 12: "media distributed on multiwell plates, and eluents matched to the respective chromatography media..."

page 6, line 3: "suitable chromatography media and the associate eluents in a very short time..."

page 8, line 1: "in the eluates of the multiparallel chromatography system."

See also:

page 10, line 4,

page 10. line 20,

page 11, lines 6 and 27-31,

page 13, lines 13-16,

page 15, line 6,

page 16, lines 9-12, 20-22 and 31,

page 17, lines 22-23,

page 18, line 9-11,

page 19, line 9-11

and especially the examples.

It is thus amply evident to one of ordinary skill in the art that the present invention is directed to determination of relevant parameters for elution chromatography, and it is submitted that the amendments to claim 1 in no way represent new matter. Withdrawal of the rejection under 35 U.S.C. § 112 is appropriate, and is respectfully requested.

Rejections under 35 U.S.C. §§ 102 and 103

Claims 1-7 and 10 have been rejected under 35 U.S.C. 102(b) or the alternative 103, over Cramer '086. Reconsideration of this rejection is respectfully requested.

It is argued, at page 2 of the Office Action, that "if a difference exists between the claims and Cramer...it would reside in optimizing the steps of Cramer...". Applicants respectfully disagree with this analysis. Cramer is directed to a method for screening "displacer candidates" for use in displacement chromatography. Patentees state, at paragraph [0005],

> displacement chromatography is fundamentally different from elution chromatography (e.g., linear gradient, isocratic or step gradient chromatography). The displacer, having an affinity higher than any of the feed components, competes effectively for adsorption sites on the stationary phase. An important distinction between displacement and desorption is that the displacer front always remains behind the adjacent feed zones in the displacement train, while desorbents (e.g., salt, organic modifiers) move through the feed zones. The implications of this are quite significant in that displacement chromatography can potentially concentrate and purify components from mixtures having low separation factors. In the case of desorption chromatography, however, relatively large separation factors are generally required to give satisfactory resolution.

Applicants moreover state that, "the essential operational feature which distinguishes

displacement from elution or desorption chromatography is the use of a displacer molecule. See paragraph [0006] of the Cramer application.

By contrast, the present claims are directed to a method for discovering suitable *elution* chromatography parameters for the separation of biological molecules, in an automated manner. In contrast to the teaching of Cramer, the matter of the present invention is based on methods of elution chromatography and it is the aim to develop a simple method to find out with minimal effort optimized conditions for purifying biological samples, preferably for the separation of biological molecules. The present invention is focused on and claims methods of ascertaining conditions of elution chromatography. This means that, in each case, the biological samples are bound to the chromatography media. Then materials (solutions and substances) are added, which are able to desorb (to elute) the biological sample from the chromatography medium in a way as described on page 3, last paragraph of the present specification. The biological sample is removed from the chromatography material but is not displaced by a further compound, unlike the situation with displacement chromatography as in Cramer.

Because the present invention involves a method for the purification of biological samples and isolation of biological molecules on a large scale, the chosen chromatography material has to be useable continuously for the purification or separation in an ongoing process. Therefore, conditions of displacement chromatography would not be suitable. Thus, Cramer, which clearly distinguishes elution chromatography from their method, does not anticipate the present claims, nor suggest them. One of ordinary skill in the art would not transfer any teachings from the displacement method of Cramer to elution chromatography, in view of the above discussed substantial differences in materials, technique and conditions.

By way of further explanation, the divergent techniques can be explained as follows.

There are three different types of liquid chromatography: 1) isocratic elution, 2) elution chromatography and 3) displacement chromatography. These types of chromatography are each carried out in entirely a different technical manner; moreover the basic physicochemistry which leads to separation is different. In the case of isocratic elution the compounds to be separated are divided from one another according to their affinities for a stationary phase and for the mobile phase. Molecules with high affinity for the stationary phase move with less speed across the

column than molecules with low affinity, because the probability of residence of molecules with high affinity for the stationary phase is higher than that for molecules which stay in the mobile phase. In consequence, the molecules are eluted according to a Gaussian bell curve.

The separation mechanisms in elution chromatography are the same as described for the isocratic elution of compounds, but with the difference that during the course of separation a second mobile phase is added. This secondary mobile phase speeds up the elution of molecules from the stationary phase by weakening or preventing the interaction between the molecules and the stationary phase. This effect is also achieved if the second mobile phase is added in big excess. Molecules of the second phase in excess shield the sample molecules, which shall be separated, from the interaction with the stationary phase. The effect is a decrease of the probability of residence of molecules with high affinity for the stationary phase and a decrease of affinity for the stationary phase.

On the other hand, in separation carried out by means of displacement chromatography, the affinity for the stationary phase stays the same during the whole separation procedure, because the separation is carried out with only one mobile phase. In displacement chromatography, a molecule with high affinity for the stationary phase or chromatography matrix (the displacer) competes effectively for bonding sites, and thus displaces all molecules with lesser affinities for the stationary phase. In order to elute the molecules, which interact with the stationary phase, a second molecule is added to the eluent in low concentration. This second molecule displaces the desired molecule from the stationary phase. The desired molecules cannot return to the bonding sites if the displacer molecules follow directly. This means, that molecules with higher affinity displace molecules with less affinity for the stationary phase.

In contrast to the mechanism of elution chromatography, in displacement chromatography the desired molecules of the sample and the displacer molecules compete for the bonding sites of the stationary phase. In order to achieve a good separation result the flow rates during displacement chromatography are reduced to a tenth of the separation techniques described above. Because of the separation mechanism during displacement chromatography the affinity for the stationary phase plays a minor role, unlike elution chromatography, where affinity for the stationary phase dominates.

The disclosure of Cramer deals with the physicochemical laws of displacement chromatography, but disregards the principles of elution chromatography. According to the teachings of Cramer, the skilled artisan is able to find suitable displacers, but gets no information allowing selection of suitable parameters for elution chromatography, as claimed in the present application. Therefore, the teaching of the present application is in no way an "optimization" of the steps of Cramer, but a complete departure therefrom, with respect to the parameters which are determined. In order to determine elution parameters, materials tested necessarily differ from Cramer's technique; Cramer needs not to test eluents for example.

Thus, although it is argued on page 5 of the final rejection that "all the steps are the same as Cramer" and concluded that the results "must be the same," in fact, the steps and results are *not* the same, inasmuch as Cramer discloses the selection of displacer molecules from a great number of compounds, but the present claims recite analyzing bound and unbound molecules of a biological sample depending upon the chromatography medium *and ascertaining elution chromatography parameters*. The reference in no way suggests the determination of elution chromatography parameters, and thus the materials employed in the reference, displacer molecules, are not suggestive of, for example, testing eluants as in the present claims. On this basis alone, it is clear that the processes of the reference do not suggest the present claims.

The final rejection argues, however, that " excluding ascertaining displacer parameters is considered to be new matter." As discussed above, this is not the case and it is submitted that, even if it were new matter, the Examiner would have to give weight to the recitation. See M.P.E.P. section 2163.06. Withdrawal of the 102/103 rejection is therefore respectfully requested.

Claims 1-7 and 10 have also been rejected under 35 U.S.C. § 103 over Cramer taken with Welch '160. It is argued, at page 3 of the final rejection, that "at best" the claims differ from Cramer in reciting elution chromatography. Welch also does not suggest the use of elution chromatography. The portions cited in the '160 patent (see page 3 of the Office Action) discuss separation of an enantiomeric pharmaceutical active substance (Naproxen®) and the screening for finding suitable adsorbents. As a result, a combination of Cramer and Welch would teach to one of ordinary skill in the art a method involving identification of a suitable adsorbent and of

suitable displacer molecules for the adsorbed molecule to be isolated. This clearly does not suggest determination of parameters for a method for the separation and purification of biomolecules as presently claimed. Withdrawal of this rejection is therefore also appropriate, and respectfully requested.

Claim 5 has also been rejected under 35 U.S.C. over Cramer taken with Welch, further in view of MacPhee '753, Snyder '242 and Pantoliano '293. This rejection has essentially been discussed previously. The secondary references are cited primarily for their disclosure of stabilization of proteins with glycerol. Regardless, it is submitted that these references do nothing to remedy the deficiencies of the primary reference, in that elution chromatography parameters are not suggested to be ascertained by the method of the primary reference. There is simply nothing in the secondary references which would teach expanding the method of the primary reference from displacement chromatography to elution chromatography. Moreover, MacPhee discloses a large number of possible stabilizers. Glycerol is one substance of the disclosed group and is not preferred. A very large list of possible stabilizers is given by MacPhee in U.S. 2003/0161753 A1 on page 4, in column 2 up to page 5, column 1, with divergent moieties listed: sugars, enzymes, fatty acids, amino acids, vitamins and so on. Furthermore, the stabilizers named by MacPhee are compounds that alone or in combination reduce damage to the biological material being irradiated to a level that is insufficient to preclude the safe and effective use of the material. This reference accordingly does not teach the use of glycerol to stabilize biomolecules in a chromatography process.

In conclusion, it is respectfully submitted that none of the references, singly or in combination suggest the present claims, and, withdrawal of all rejections is respectfully requested. The claims of the application are submitted to be in condition for allowance. However, if the Examiner has any questions or comments, he is cordially invited to telephone the undersigned at the number below.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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